Stereotactic image-guided lung radiotherapy (SBRT) for clinical early-stage NSCLC: a long-term report from a multi-institutional database of patients treated with or without a pathologic diagnosis

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Abstract: PURPOSE: Early stage lung cancer is treated with stereotactic body radiation therapy (SBRT) in patients who are unable or unwilling to undergo surgical resection. Some patients' comorbidities are so severe that they are unable to even undergo a biopsy. A clinical diagnosis without biopsy before SBRT has been used, but there are limited data on its efficacy. METHODS AND MATERIALS: Data on patients treated with SBRT for non-small cell lung cancer, with and without tissue confirmation, were collected from multiple institutions across Europe, Canada, and the United States. Patients with a minimum of 2 years of comprehensive follow up were selected for analysis. Treatment and patient characteristics were compared. Overall survival (OS), disease-free survival (DFS), cause-specific survival (CSS), and rates of local recurrence (LR), regional recurrence (RR), and distant metastasis (DM) were calculated and analyzed. RESULTS: A total of 701 patients were identified, of which 67% had tissue confirmation of their tumors. The 3- and 5-year outcomes for OS, CSS, and DFS were 83.8%, 93.1%, 69%, and 60.6%, 86.7%, 45.5%, respectively. The rates for LR, RR, and DM at 3 and 5 years were 6.4%, 9.3%, 14.3%, and 10.5%, 14.3%, 19.7%, respectively. There were no statistically significant differences in survival outcomes or recurrences between the biopsy and no-biopsy cohorts. CONCLUSIONS: SBRT for clinically diagnosed lung cancers is efficacious in appropriately selected patients, with similar outcomes as those with a pathologic diagnosis. Thorough clinical and radiographic evaluations in a multidisciplinary setting are critical to the management of these patients.

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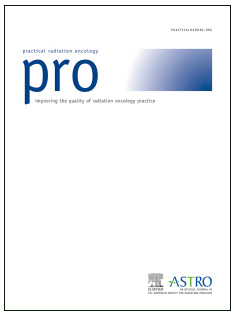

Stereotactic image-guided lung radiotherapy (SBRT) for clinical early-stage NSCLC: A long-term report from a multi-institutional database of patients treated with or without a pathologic diagnosis.

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Title

Stereotactic image-guided lung radiotherapy (SBRT) for clinical early-stage NSCLC: A long-term report from a multi-institutional database of patients treated with or without a pathologic diagnosis.

Short Title

SBRT outcomes in clinically diagnosed NSCLC.

Authors

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Conflict of Interest Statement

Dr. Hope, Dr. Kestin, and Dr. Grills report either financial and/or non-financial support from Elekta during or outside the conduct of the study. Elekta had no input in data collection, analysis, interpretation, or writing of this manuscript. The remaining authors whose names are listed certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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Abstract

Objective

Early stage lung cancer is treated with stereotactic body radiotherapy (SBRT) in patients unfit or unwilling to undergo surgical resection. Some patients' comorbidities are so severe that they are unable to even undergo biopsy. Clinical diagnosis without biopsy before SBRT has been utilized, but there are limited data on its efficacy.

Methods

Data on patients treated with SBRT for non-small cell lung cancer (NSCLC), with and without tissue confirmation, were collected from multiple institutions across Europe, Canada, and the United States. Patients with a minimum of two years of comprehensive follow up were selected for analysis. Treatment and patient characteristics were compared. Overall survival (OS), disease-free survival (DFS), cause-specific survival (CSS), rates of local recurrence (LR), regional recurrence (RR), and distant metastasis (DM) were calculated and analyzed.

Results

Seven hundred one patients were identified, of which 67% had tissue confirmation of their tumors. OS, CSS, and DFS three and five-year outcomes were 83.8%, 93.1%, 69%, and 60.6%, 86.7%, 45.5%, respectively. LR, RR, and DM rates at three and five-years were 6.4%, 9.3%, 14.3%, and 10.5%, 14.3%, 19.7%, respectively. There were no statistically significant differences in survival outcomes or recurrences between the biopsy and no biopsy cohorts.

Conclusions

SBRT for clinically diagnosed lung cancers is efficacious in appropriately selected patients, with

similar outcomes as those with pathologic diagnosis. Thorough clinical and radiographic evaluation in a multidisciplinary setting is critical to the management of these patients.

Introduction

Lung cancer is the second most common non-cutaneous malignancy in the United States, with the highest mortality rate.[1] The vast majority of cases are non-small cell lung cancer (NSCLC), with 60% - 70% of patients presenting with locally advanced or metastatic disease, and only 20 – 30% as early-stage.[2,3] Even in early-stage disease, untreated NSCLC has a poor prognosis, with a median survival time of just over one year.[4–6] The standard of care for early-stage disease is lobectomy and mediastinal lymph node dissection.[7] However, a high incidence of comorbidities often results in patients being unable to undergo curative resection.

Stereotactic body radiotherapy (SBRT) utilizes highly conformal, high dose per fraction radiation therapy, often used in early-stage NSCLC patients, with trials both domestically and abroad demonstrating excellent local control rates.[8–11] This is a highly favorable treatment option for medically inoperable patients, which has been demonstrated to be safe in elderly patients and those with poor pulmonary function.[12–14] Unfortunately, some patients have significant comorbidities precluding tumor biopsy for tissue confirmation, or they decline to undergo biopsy.[15]

Recognizing this limitation, the utilization of SBRT in clinically diagnosed patients (i.e., without biopsy) has been growing, most pronounced in Europe, with the largest study comparing patient outcomes with or without tissue confirmation reported from the Netherlands and showing similar treatment results between two cohorts.[16] In the US as well, there has been an increase in SBRT utilization for clinically diagnosed lung cancer in elderly and medically inoperable

patients.[17,18] Although SBRT is generally considered safe, it does carry with it a certain risk of side effects and toxicity, and must be delivered judiciously. There is also concern that improper patient selection may result in overtreatment of incidentally detected, slow growing lesions.[19] Indeed, there have been efforts to improve patient selection to minimize unnecessary therapy.[16,20] While the Dutch analysis demonstrated equivalent outcomes, the patients were derived from a homogenous population at a single institution, and the generalizability of the results remains uncertain.

Our group has previously published on the efficacy of image-guided SBRT for early-stage NSCLC with high rates of local control and acceptable rates of toxicity.[11] In this report, we studied the outcomes of SBRT for clinically diagnosed NSCLC lesions with and without pathologic confirmation.

Materials and Methods

Patients and Work-Up

Patients treated between 2004 – 2014 across five international institutions (Xxxxxxx Xxxxxxxx Xxxxxxxx, Xxxxx Xxx, Michigan; Xxxxxxxxxx Xxxxxxxx Xxxxxxxx, Xxxxxxxx, Germany; Xxxxxxxxxxx Xxxxxx Xxxxxxxxx, Xxxxxxxxx, Netherlands; Xxxxxxx Xxxxxxxx Xxxxxxxx, Xxxxxxx, Xxxxxxx, Canada; and Xxxxxx Xxxxxxxxx Xxxxxxxxxx Xxxxxxxx, Xxxxxxxxxxxx, Pennsylvania) were included. Patient workup included at a minimum: history, physical examination, computed tomography (CT) scans of the chest and upper abdomen, including liver and adrenals, and serum chemistries. 18-fluorodeoxyglucose positron emission tomography (18FDG-PET) scans and pulmonary function tests (PFTs), and any additional workup was performed at the discretion of the respective institutions, including bone scans and

brain imaging. Tissue confirmation was obtained based on multiple factors including patient risk, biopsy difficulty, patient willingness, etc. Method of primary and lymph node biopsy, and diagnosis in the absence of tissue biopsy, was at the discretion of each institution's oncology and multidisciplinary teams. Exclusion criteria included metastatic disease, greater than ten fractions radiation therapy, and non-NSCLC histology.

Treatment and Follow-Up

Technical details of SBRT delivery were described in a previous publication.[11] Briefly, all patients underwent CT simulation with 3D planning, with 4D scans to account for tumor motion required starting in 2006. Immobilization techniques differed between institutions including stereotactic body frame, supine position without custom immobilization, and other immobilization techniques. All institutions delineated the gross tumor volume (GTV) using CT lung windowing with mediastinal windowing as needed for lesions abutting a pleural surface. The internal target volume (ITV) was based on a 4D scan. Any clinical target volume (CTV) expansion was done at the discretion of each institution's policies, and a minimum planning target volume (PTV) of 0.5cm was employed. Treatment was typically delivered with 6 MV photons using between 5-12 beams with segments, including both coplanar and non-coplanar arrangements. Heterogeneity correction was used for dose calculation and analysis, with a volumetric prescription to the PTV edge. Prescription dose and fractionation was at each respective institution's discretion. Normal tissue constraints were based on institution policy or Radiation Therapy Oncology Group (RTOG) guidelines. All patients on treatment underwent daily cone-beam computed tomography (CBCT) for imaging verification.

All patients underwent routine follow up with a minimum of thoracic CT scans obtained every three to six months during the first two years, with the incorporation of 18FDG-PET at the

discretion of the institution. Evaluation of recurrence was based on serial CT chest, 18FDG-PET, and biopsy when feasible. The follow up period was defined from end of SBRT until last follow up or death. Local recurrence was defined as occurring within the treatment volume; regional recurrence within regional lymph nodes, and distant recurrence elsewhere. Toxicity evaluation was based on National Cancer Institute Common Toxicity Criteria Version 3.

Statistical Analysis

Each institution received local IRB approval. The details of patient characteristics, treatment specifics, clinical outcomes, and toxicity were verified before anonmyziation and analysis. Only those patients with a minimum of two years of follow up were used for the analysis of overall survival (OS), cause-specific survival (CSS), disease-free survival (DFS), local recurrence (LR), regional recurrence (RR), and distant metastases (DM). This was done to ensure robust outcome data and to highlight detectable signals in recurrence patterns, which has particular importance when analyzing biopsied vs. not-biopsied tumors. Student's unpaired t-test and Pearson's chi-squared exact test were used to compare continuous and categorical variables among groups, respectively, to evaluate potential discrepancies among patient subgroups concerning patient, treatment, or tumor-related factors. Analyses of DFS, CSS, and OS were calculated and compared using the Kaplan–Meier method. Estimates of LR, RR, and DM were calculated using the competing risk method. Doses were standardized for analysis based on biological equivalent doses ($BEDGy_{10}$). Univariate and multivariate analyses were performed using the Cox Regression model. Findings were considered statistically significant if the p-value was <0.05 or if 95% confidence interval (CI) did not encompass one, and all statistical tests were two-sided. Additional analyses looking at outcomes by size, synchronous, and metachronous lesions were done to better characterize disease characteristics. Statistical analyses were

performed with SPSS Version 24.0 (IBM, Armonk, NY, USA) and R software (RStudio Inc., Boston, MA).

Results

Patient Characteristics

Of the entire cohort, 701 patients with 752 tumors (58.4%) had follow up of at least two years, with a median follow up of 3.7 years (range 2.0 – 11.4). Median patient age was 74 years (range 42.0 – 93.5) and 87.9% were considered inoperable with a Karnofsky Performance Status of 80. PFTs were obtained in 88% of patients, with median forced expiratory volume in one second (FEV1) of 1.63L (56.9% predicted), and median diffusing capacity for carbon monoxide (DLCO) of 9.73ml/min/mmHg (51.7% predicted). Typical tumors had a maximum diameter of 2.0cm (range 0.5 – 9.6), and were peripheral as per the RTOG 0236 definition (88.4%).[8] 18FDG-PET staging was completed in 94.8% of patients. A detailed list of patient and lesion characteristics are available in Table 1.

T-test comparison of patient factors between the "biopsy" and "no biopsy" groups revealed statistically significant differences and are listed in Table 2. In general, higher mean values were present in the biopsy group for age, baseline 18FDG-PET maximum standardized uptake value (SUVmax), tumor size, lymph node evaluation, and number of fractions/treatment days ($p<0.05$). Only number of peripheral lesions was higher in the no biopsy cohort (86.3% vs 93.1%, $p=0.01$).

Treatment Details

4D CT simulation was performed in 86.3% of patients, and CBCT image guidance before each fraction was utilized in 100% of SBRT deliveries. Median prescription dose to the PTV was

54.0Gy (range 26 – 60) in 3 fractions (range 1 – 10), with median $BEDGy_{10}$ to the PTV of 144Gy (range 60 – 180). Median lung V20 (volume of lung not including GTV receiving 20Gy or greater) was 6.0% (range 0 – 40). Analysis of dosimetric variables between the biopsy and no biopsy groups (Table 2) revealed higher prescription dose, Dmean (mean dose delivered), Dmax (maximal dose delivered) and Dmin (minimal dose delivered) to the GTV and PTV for the no biopsy group ($p<0.01$). There was no difference in lung V20Gy (volume of lung receiving 20Gy or greater), but higher lung Dmean ($p<0.01$) in the biopsy group.

Outcomes and Analysis

The 3- and 5-year LR, RR, and DM rates for all patients with at least two years of follow up were 6.4%, 9.3%, 14.3%, and 10.5%, 14.3%, 19.7%, respectively. OS, CSS, and DFS at 3- and 5-years for all patients with at least two years of follow up were 83.8%, 93.1%, 69%, and 60.6%, 86.7%, 45.5%, respectively. There were no significant differences in recurrence (Figures 1a, 1b, 1c) or survival rates (Figures 2a, 2b, 2c) between the biopsy vs. no biopsy groups (Table 3). Consistently demonstrated between both cohorts were high mortality rates as a competing risk event to local, regional, and distant recurrence (Figures 1a, 1b, 1c). Univariate analysis evaluating risk factors for LR based on tumor and treatment factors did not reveal any significant factors ($p>0.05$), although lymph node tissue evaluation with an HR of 2.28 (95% CI 0.91 – 5.70, $p=0.08$), and administration of chemotherapy with an HR of 2.68 (95% CI 0.97 – 7.38, $p=0.06$) were trending for significance (Table 4). Analysis of OS and CSS including patients with less than 2 years of follow up did not reveal significant differences ($p>0.05$) between the biopsy and no biopsy cohorts suggesting no selection bias by our selection criteria (Supplementary 1). Analysis of LR, RR, DM based on size (≤2cm vs. >2cm) revealed nearly significant higher rates of local recurrence ($p=0.08$), but no statistically significant differences in

RR and DM ($p>0.1$). Patients with synchronous or metachronous tumors did not have significantly higher rates of RR ($p>0.05$), but both had significantly higher rates of DM compared to those with a single tumor ($p<0.01$). Figures and analyses are available in the supplementary (Supplementary 2, 3, 4).

Discussion

Our study demonstrates that appropriately selected patients with clinically diagnosed, early-stage NSCLC who are unable or unwilling to undergo tissue confirmation derive similar outcomes after SBRT as patients with biopsy-confirmed tumors. This benefit was not limited to local control and OS, and also included similar rates of RR, DM, and CSS. These other endpoints are particularly notable as they reinforce the hypothesis that patient selection for SBRT without biopsy was appropriate. Clinical differences between the cohorts were minimal. Dosimetric differences were notable for higher $BEDGy_{10}$ in the no biopsy cohort (Table 2). However, median prescription and Dmean $BEDGy_{10}$ in both cohorts were well above 100 BEDGy10 which is considered the necessary threshold to obtain the high rates of local control quoted in modern trials and series.[10,11]

We focused our analysis on patients with a minimum of two years of follow up. This was done to confirm comprehensive follow up length for analysis, and to evaluate patients who would most benefit from treatment as competing comorbidities/risk factors for death are well established in this patient group. In addition, longer follow up is associated with greater rates of regional and distant failure,[21] and would potentially highlight discordance between the cohorts if benign lesions were treated in the no biopsy cohort. Despite this, our rates of LR, RR, and DM were similar to those reported by Verstegen et al. from the Netherlands.[16] While our rates of OS were higher than those reported in their report (3yr-OS 83.8% vs. 55.4%), this may be a result of

our minimum two-year follow-up requirement rather than unique treatment outcomes. Comparison to our unselected cohort suggests similar survival (Supplementary 1), and there was no difference between the biopsy and no biopsy groups. When comparing our results to prospective trials with long term follow up, our 5 year local, regional, and distant recurrence rates are similar to those reported by Timmerman et al. and Sun B et al. (~8%, ~11%, 11-24%).[21,22]

Rates of empiric SBRT therapy have steadily increased nationally in the United States, estimated to be greater than 5% in 2011, with rates likely to have increased since then.[18] This greater willingness to use the modality by radiation oncologists is likely a manifestation of increased experience with SBRT, overall low levels of toxicity observed, as well as higher rates of referrals once general awareness increased among other physicians. While tissue biopsy confirmation is always preferable, this may not be feasible in in those who refuse biopsy, have undergone non-diagnostic biopsy, or who may carry prohibitive risk with biopsy. Indeed, official American Society of Radiation Oncology (ASTRO) guidelines for SBRT in patients with early NSCLC recognize the appropriateness of empiric treatment in this patient population, after exhausting efforts to obtain biopsy, with a recommendation strength of "strong" and a 100% committee consensus.[23]

Treatment of patients with clinically diagnosed early-stage lung cancer requires careful staging and risk stratification. There are multiple guidelines by various organizations and societies to help guide evaluation and management of pulmonary nodules, including those from the Fleischner Society, American College of Chest Physicians (ACCP), International Association for the Study of Lung Cancer (IASCL), American College of Radiology (ACR) Lung-RADS system, and British Thoracic Society.[24–27] Consistent across these guidelines is an emphasis on

clinical and radiographic characteristics considered in a multidisciplinary setting. Incorporation of PET scans into risk stratification models of pulmonary nodules has been shown to increase sensitivity and receiver operating characteristic (ROC) curves.[28] Proper risk stratification is paramount, with ACCP guidelines recommending a pre-test probability cutoff of >65% to consider surgical diagnosis, while other models have suggested higher cutoffs as high as 85% for empiric PET scan-directed SBRT.[20,25,29] A recent publication by the Lung Cancer Collaborative Group suggested guidelines in the empiric use of SBRT for NSCLC including workup and treatment considerations, with specific recommendations for suspected tumors >3cm vs. ≤3cm vs. ground glass nodules.[30] The management of patients unfit or unwilling to undergo biopsy for suspected NSCLC will become only more sophisticated in the future with the refinement of circulating tumor cells and DNA, known as "liquid biopsies," in risk stratification.[31,32]

Probability calculators have also been developed to provide more quantitative measures for physicians. These calculators include Mayo Clinic, Veterans Association, Pan-Canadian Early Detection of Lung Cancer Study (PanCan), and Vrije Universiteit (VU) models.[33–36] Similar to society guidelines, these calculators take into consideration patient demographics and radiographic characteristics, with the VU model also incorporating FDG avidity on PET scans. Validation studies of those calculators demonstrated good accuracy in the Mayo and PanCan models, with the highest accuracy seen with 18FDG-PET scan information in the VU model.[37] In general, these models describe older patients with large, solid, spiculated, PET-avid lesions in the upper lobe in the setting of prior cancer and tobacco use being at the highest risk of malignancy. A limitation of these tools is their inability to take into consideration confounding in areas and populations with high rates of benign radiographic findings.[38] Examples would be areas and populations with high rates of tuberculosis, histoplasmosis, blastomycosis,

coccidioidomycosis, etc. In a meta-analysis by Deppen et al, 70 studies evaluating 8,511 nodules were analyzed in the PET staging era.[39] When analyzing studies in areas with endemic infectious lung disease, specificity was found to be 16% lower. This may pose a particular issue in parts of the United States where granulomatous fungal infections occur commonly. Ultimately, this reinforces the need for careful risk stratification based on clinical and radiographic information in a multidisciplinary manner by physicians familiar with the respective patient population.

Prior reports on the subject have consistently demonstrated largely equivalent outcomes between biopsy and no biopsy groups. The largest series was the Dutch report with nearly 600 patients with over 30 months median follow up, 65% treated empirically, with no differences in OS or disease control.[16] Single institution experiences in the United States have also been reported, with largely consistent results. Wegner et al. published their experience at Allegheny General Hospital in Pittsburgh, PA with 196 patients, 51% without biopsy, with a median follow up of 17 months, with no difference in OS, LR, RR, or DM.[40] Haidar et al. at the University of California San Diego reported SBRT outcomes of 55 patients, 41% without biopsy.[41] With a median follow up of 25.8 months, they reported no significant differences in OS. While these reports together are reassuring, they are restricted in their generalizability due to their largely single institution nature, homogenous patient populations or low patient number with limited follow up. This concern was highlighted in the meta-analysis by IJsseldijk et al. which compared 43 studies with over 11,000 patients with clinically or pathologically diagnosed early-stage NSCLC treated with SBRT. Comparative and pooled analysis generally revealed lower OS, CSS, and DFS in the biopsy diagnosed group.[42] The studies included in their analysis did not all utilize PET-CT staging, emphasizing the need for vigorous work-up and staging to properly risk-stratify patients.

Our study has several strengths worthy of discussion. Patients in our study were nearly all 18FDG-PET staged, increasing diagnostic probability using modern staging methods. All patients were treated with 3D, volumetrically prescribed, image-guided radiotherapy (IGRT) via CBCT. Analyses of all dose-volume relationships and clinical outcomes were based on heterogeneity-corrected dose. Seven hundred fifty lesions in 701 patients with a median follow-up of nearly four years were reported, greater than those listed in the Dutch study and the largest data set available. Our results represent the experiences of multiple, international institutions across Europe and North America, increasing the potential for generalizability.

Limitations of our study should also be taken into consideration when interpreting our results. Around 44% of reported lesions were treated in the Netherlands, representing a significant proportion of patients. Patient risk stratification and decision to pursue treatment was done at the discretion of each respective institution's oncology and multidisciplinary teams, with no uniform probability metric or cutoff. There was a wide range of SBRT techniques utilized in our study that is reflective of the efforts of early adopters of SBRT due to a proportion of our patients that were treated before the publication of RTOG 0236 and standardization of techniques.[8] This should not impact the overall efficacy of treatment and is present in both cohorts. We were not able to evaluate if there were ground glass lesions treated in the no biopsy cohort, and the lack of tissue diagnosis may have allowed for treatment of very early stage small cell lung cancer and/or treatment of more indolent forms of adenocarcinoma which may influence urgency of treatment.[43–45] However, time from 18FDG-PET to treatment (Table 2) was not significantly different between our cohorts. We do not have data on rates of subsequent malignancies after treatment which have been noted to be up to 10% in the literature, and may confound the no biopsy cohort.[46] PET/CT staging should have minimized the misdiagnosis of

head and neck primaries that presented with pulmonary lesions. We did not have explicit information on T3/4 lesions based on separate lung nodules which might have had different rates of RR and DM. We did report on the rate of synchronous and metachronous rates in each cohort, and analysis did not reveal significant difference (Table 2). Continued smoking after diagnosis and treatment of lung cancer has been noted to affect treatment outcomes and was not available in our data set.[47] Toxicity or quality of life data was not recorded although prior studies in the elderly and patients with significant co-morbidities have been previously reported.[12,14]

Conclusion

SBRT for clinically diagnosed early-stage NSCLC provides efficacious and equivalent outcomes in appropriately selected patients when compared to those with a pathologic diagnosis. Patients being considered for empiric SBRT should undergo comprehensive risk stratification incorporating clinical and radiographic information, in a multidisciplinary setting.

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Table 1. Patient and Lesion Characteristics

FEV1 – forced expiratory volume in one second, DLCO – diffusing capacity for carbon monoxide, $BEDGy_{10}$ – biological equivalent dose using and alpha/beta of 10Gy, 4DCT – 4 dimensional computed tomography, CBCT – cone beam computed tomography, Lung V20Gy – volume of lung receiving 20Gy or greater.

Table 2. Comparison of Cohort Variables

FEV1 – forced expiratory volume in one second, DLCO – diffusing capacity for carbon monoxide, PET – positron emission tomography, SUVmax – maximum standardized uptake value, GTV – gross tumor volume, PTV – planning target volume, Dmean – mean target dose, Dmax – maximal target dose, Dmin – minimum target dose, Lung V20Gy – volume of lung receiving 20Gy or greater.

Table 3. Recurrences and Survival Outcomes by Year

Table 4. Univariate and Multivariate Analysis of Local Recurrence

SUVmax – maximum standardized uptake value, PET – positron emission tomography, RT – radiotherapy, GTV – gross tumor volume, PTV – planning target volume, $BEDGy_{10}$ – biological equivalent dose using and alpha/beta of 10Gy.

Figure 1. Control Rates and Competing Risk of Death

Comparison of local recurrences (1a), regional recurrences (1b), and distant metastases (1c) for patients with and without biopsy proven disease. Mortality rates shown to demonstrate competing risk. All p-values >0.1.

Figure 2. Survival Data Comparisons

Comparison of overall survival (2a), disease free survival (2b), and cause specific survival (2c) for patients with and without biopsy proven disease. All p-values >0.1.

Table 1. Patient and Lesion Characteristics

Characteristics		Values
Median Age		74.2 (42 - 93.5)
Sex		
Male		379 (50.4%)
Female		373 (49.6%)
Karnofsky Performance Status		80 (40 - 100)
Prior Lung Cancer		80 (10.6%)
Pulmonary Function Test		88%
FEV1 Liters (% predicted)		1.63 (56.9%)
DLCO ml/min/mm (% predicted)		9.73 (51.7%)
PET Staging		
Yes		713 (94.8%)
No		39 (5.2%)
Biopsy		
Yes		504 (67%)
No		248 (33%)
Mediastinal Evaluation		
Yes		48 (6.4%)
No		704 (93.6%)
Location (RTOG 0236)		
Central		86 (11.4%)
Peripheral		665 (88.4%)
Unknown		1 (0.2%)
Histology (if biopsied)		
Adenocarcinoma		48.5%
Squamous		30.6%
Other		20.9%
Treatment Parameters		
Dose (Gy)		54.0 (26 - 60)
Fractions		3 (1 - 10)
Median $BEDGy_{10}$		144 (60 – 180)
4DCT		86.3%
CBCT		100%
Median Lung V20Gy		6.0%
Adjuvant Chemotherapy		2.7%
Follow Up (years)		3.7 (2 - 11.4)
Lesions by Institution		
William Beaumont Health		142 (18.9%)
Thomas Jefferson University Hospital		44 (5.9%)
Netherlands Cancer Institute		340 (45.2%)
Princess Margaret Hospital		189 (25.1%)
University Hospital Würzburg		37 (4.9%)

FEV1 – forced expiratory volume in one second, DLCO – diffusing capacity for carbon monoxide, $BEDGy_{10}$ – biological equivalent dose using and alpha/beta of 10Gy, 4DCT – 4 dimensional computed tomography, CBCT – cone beam computed tomography, Lung V20Gy – volume of lung receiving 20Gy or greater.

Table 2. Comparison of Cohort Variables

Variables	Biopsy (n=504)	No Biopsy (n=248)	p-value
Age	74.1	72.2	**0.01**
Treatment Duration (days)	7.9	7.3	**<0.01**
Follow-Up (years)	4.11	3.9	0.1
FEV1 (% predicted)	57.2	56.3	0.7
DLCO (% predicted)	51.3	52.6	0.6
Days from PET to Treatment	48.7	49.0	0.92
Staging PET (%)	94.2	96	0.38
Baseline SUVmax	7.1	5.9	**0.02**
Peripheral location (%)	86.3	93.1	**<0.01**
Mediastinal Evaluation (%)	4.8	0.8	**<0.01**
Prior Lung Cancer (%)	9.1	13.7	0.22
Synchronous Lesions (%)	9.5	13.3	0.13
Metachronous Tumor (%)	11.9	13.7	0.48
Max Dimension (cm)	2.4	2.0	**<0.01**
Median Prescription $BEDGy_{10}$	132	151	**<0.01**
Fractions	3.9	3.4	**<0.01**
GTV Dmean ($BEDGy_{10}$)	187.7	220.2	**<0.01**
GTV Dmax ($BEDGy_{10}$)	196.4	220.5	**<0.01**
GTV Dmin ($BEDGy_{10}$)	150.5	169.6	**<0.01**
PTV Dmean ($BEDGy_{10}$)	167.7	191.5	**<0.01**
PTV Dmax ($BEDGy_{10}$)	190.8	212.1	**<0.01**
PTV Dmin ($BEDGy_{10}$)	98.8	108.4	**<0.01**
Lungs V20Gy (%)	6.1	5.8	0.47
Lungs Dmean (Gy)	3.5	1.5	**<0.01**
Adjuvant Chemotherapy (%)	3.4	1.2	0.1

FEV1 – forced expiratory volume in one second, DLCO – diffusing capacity for carbon monoxide, PET – positron emission tomography, SUVmax – maximum standardized uptake value, GTV – gross tumor volume, PTV – planning target volume, Dmean – mean target dose, Dmax – maximal target dose, Dmin – minimum target dose, Lung V20Gy – volume of lung receiving 20Gy or greater.

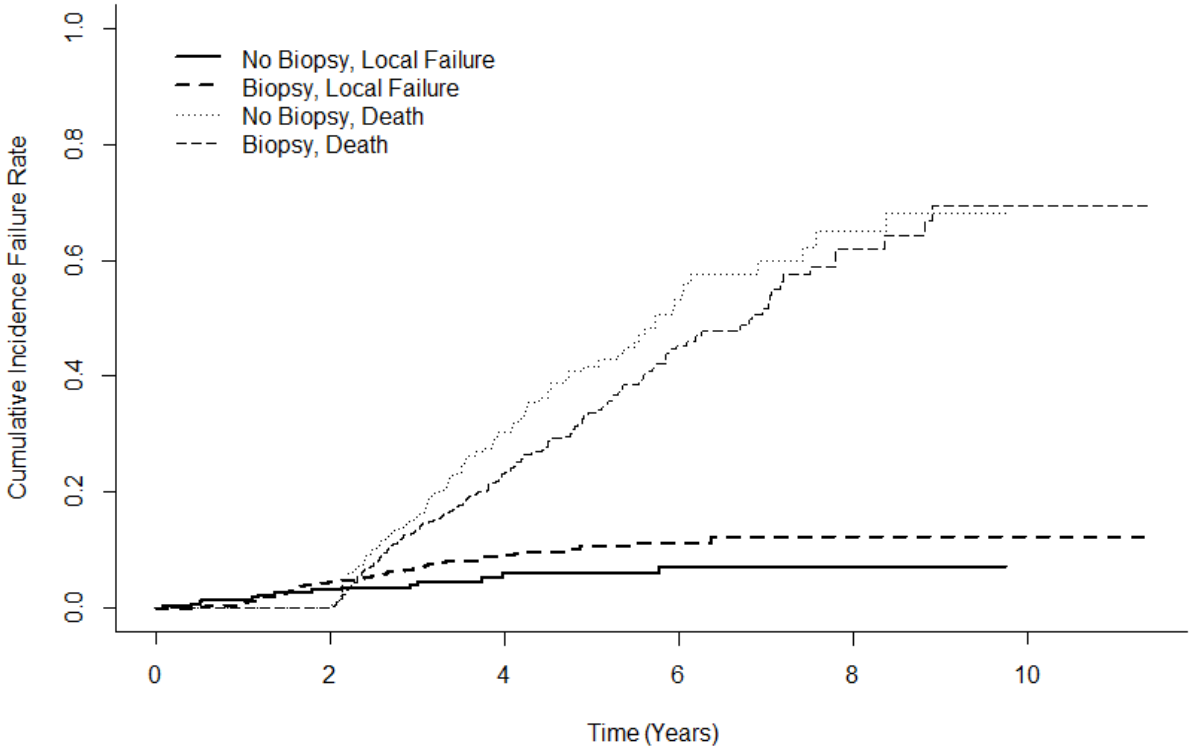
Table 3. Recurrences and Survival Outcomes by Year

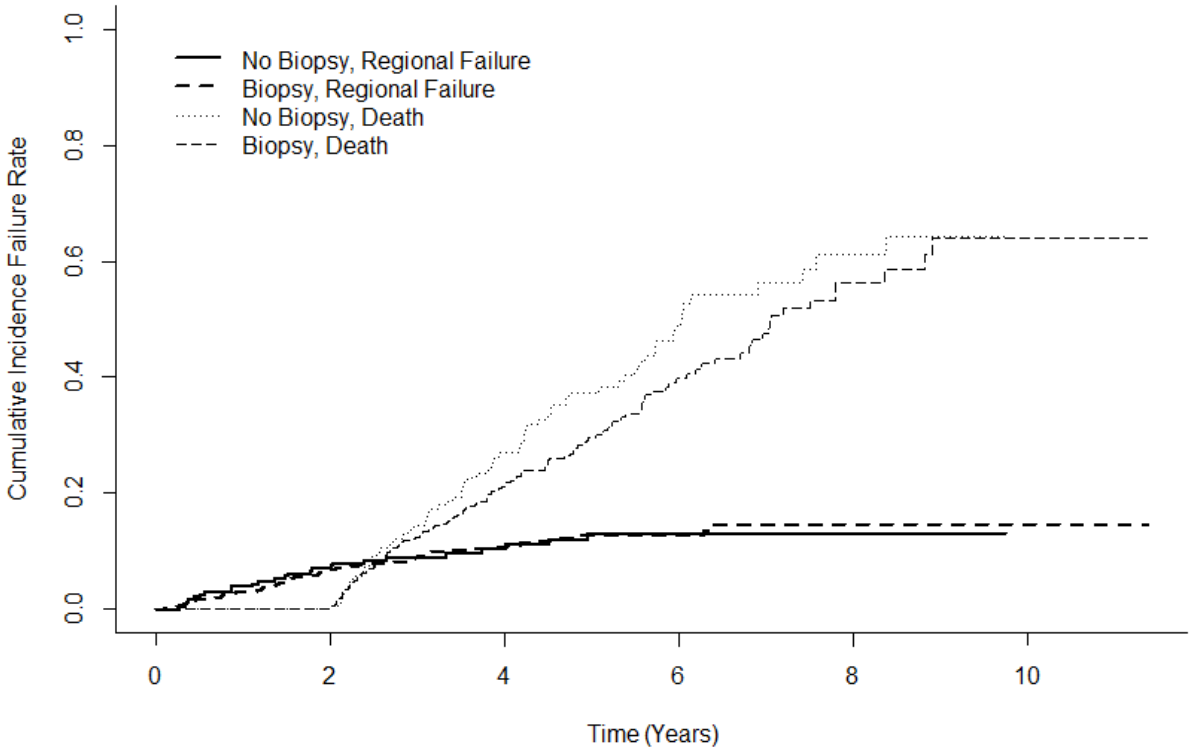
	Year	Biopsy	No Biopsy	p-value
% Local Recurrence	1-Yr	0.6	1.6	0.10
	2-Yr	4.6	3.2	
	3-Yr	7.5	4.2	
	4-Yr	9.9	5.8	
	5-Yr	12.1	6.8	
% Regional Recurrence	1-Yr	3.0	4.0	0.99
	2-Yr	7.0	7.1	
	3-Yr	9.3	9.1	
	4-Yr	11.4	10.9	
	5-Yr	14.0	15.1	
% Distant Metastases	1-Yr	3.6	5.8	0.38
	2-Yr	9.7	12.5	
	3-Yr	13.6	16.7	
	4-Yr	16.5	19.8	
	5-Yr	20.3	23.9	
% Cause Specific Survival	1-Yr	100	100	0.43
	2-Yr	100	100	
	3-Yr	92.9	93.6	
	4-Yr	90.5	90.2	
	5-Yr	86.6	87.0	
% Disease Free Survival	1-Yr	93.7	91.6	0.64
	2-Yr	83.2	83.0	
	3-Yr	69.7	67.7	
	4-Yr	58.6	56.0	
	5-Yr	46.5	43.9	
% Overall Survival	1-Yr	100	100	0.24
	2-Yr	100	100	
	3-Yr	83.8	83.6	
	4-Yr	73.8	70.0	
	5-Yr	62.6	60.0	

Table 4. Univariate and Multivariable Analysis for Local Recurrence

Variable	UVA (p-value)	Hazard Ratio (95% CI)	MVA (p-value)	Hazard Ratio (95% CI)
Max Tumor Dimension	0.69			
Baseline SUVmax	0.23		0.45	
Histology (for biopsy group)	0.31		0.28	
PET Staging (yes vs no)	0.43			
Operable (yes vs no)	0.94			
RT Dose (continuous)	0.35			
Central vs. Peripheral (RTOG 0236)	0.23			
Mediastinal Evaluation (yes vs no)	0.08	2.28 (0.91-5.70)	0.08	2.03 (0.91-4.55)
Biopsy Done (yes vs no)	0.11		0.26	
Gender (female vs male)	0.63			
Chemotherapy Received (yes vs no)	0.06	2.68 (0.97-7.38)	0.12	
GTV Mean $BEDGy_{10}$	0.35		0.24	
PTV Mean $BEDGy_{10}$	0.52			
Previous Tumor (yes vs no)	0.59			

SUVmax – maximum standardized uptake value, PET – positron emission tomography, RT – radiotherapy, GTV – gross tumor volume, PTV – planning target volume, $BEDGy_{10}$ – biological equivalent dose using and alpha/beta of 10Gy.


No Biopsy, Local Failure
Biopsy, Local Failure
No Biopsy, Death
Biopsy, Death
Cumulative Incidence Failure Rate
0.0
0.2
0.4
0.6
0.8
1.0
0
2
4
6
8
10
Time (Years)


No Biopsy, Regional Failure
Biopsy, Regional Failure
No Biopsy, Death
Biopsy, Death
Cumulative Incidence Failure Rate
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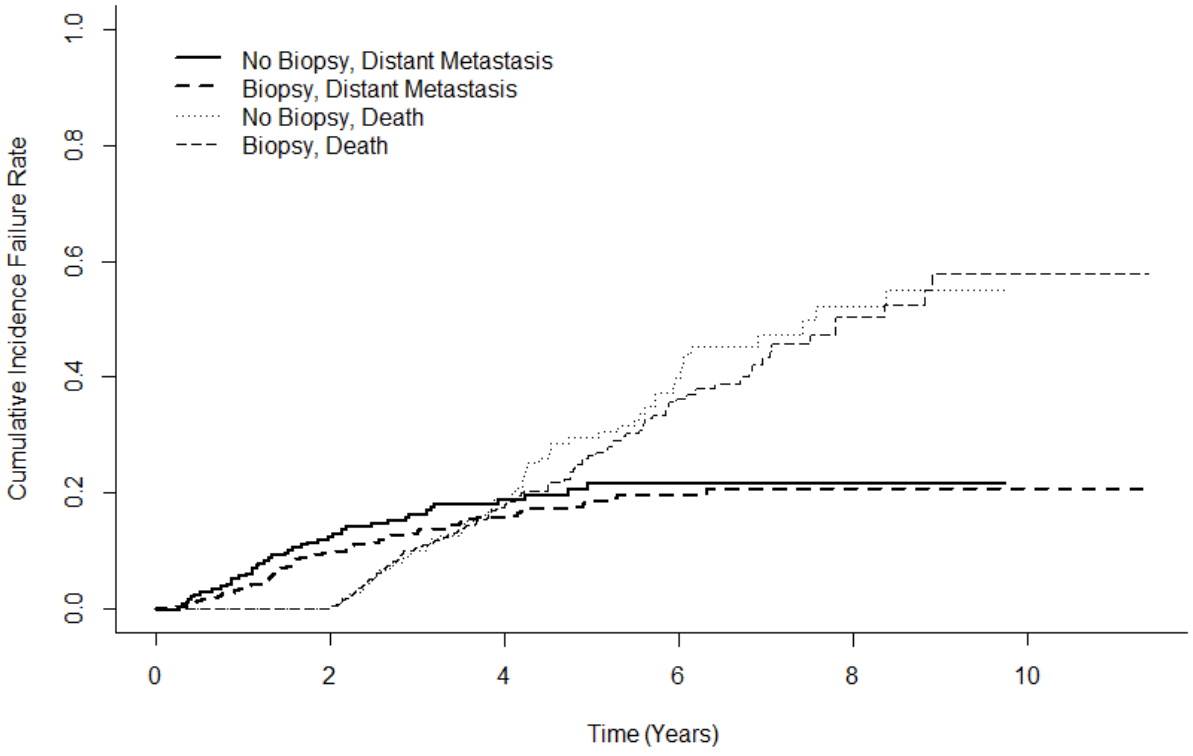
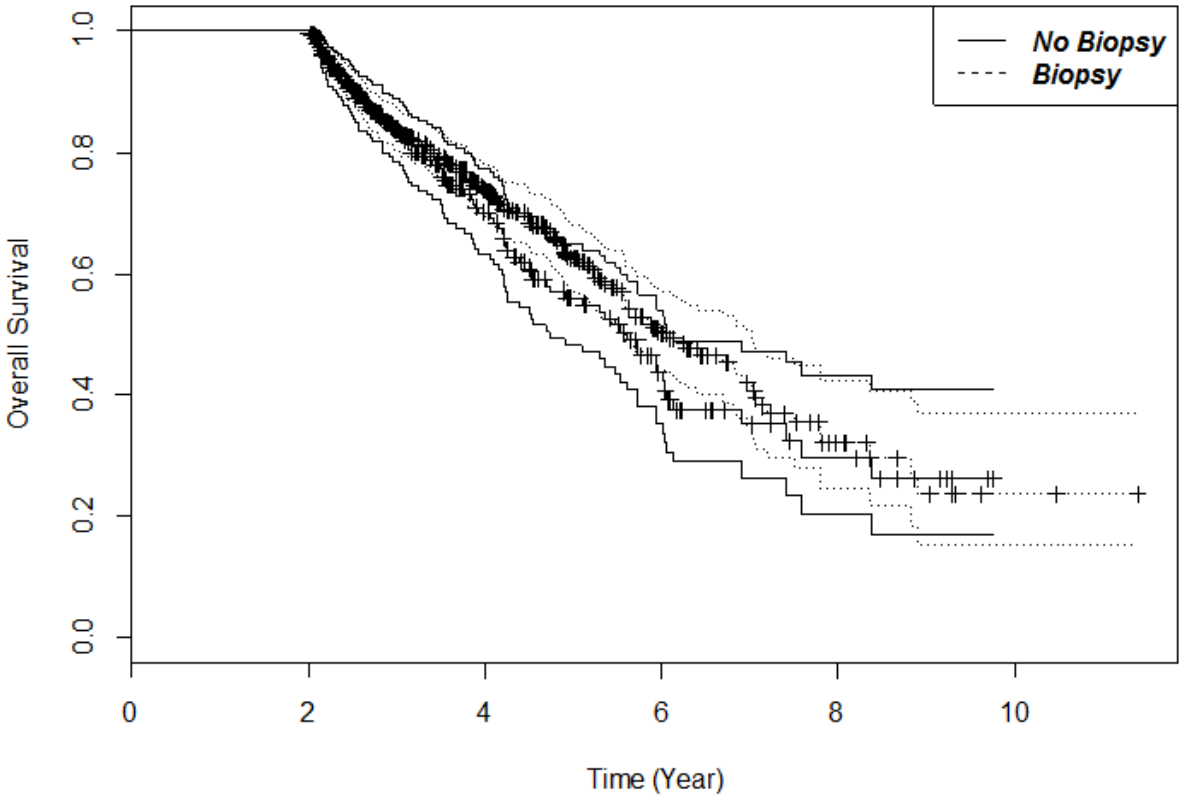
0.4
0.6
0.8
1.0
0
2
4
6
8
10
Time (Years)


No Biopsy, Distant Metastasis
Biopsy, Distant Metastasis
No Biopsy, Death
Biopsy, Death
Cumulative Incidence Failure Rate
0.0
0.2
0.4
0.6
0.8
1.0
0
2
4
6
8
10
Time (Years)


No Biopsy
Biopsy
Overall Survival
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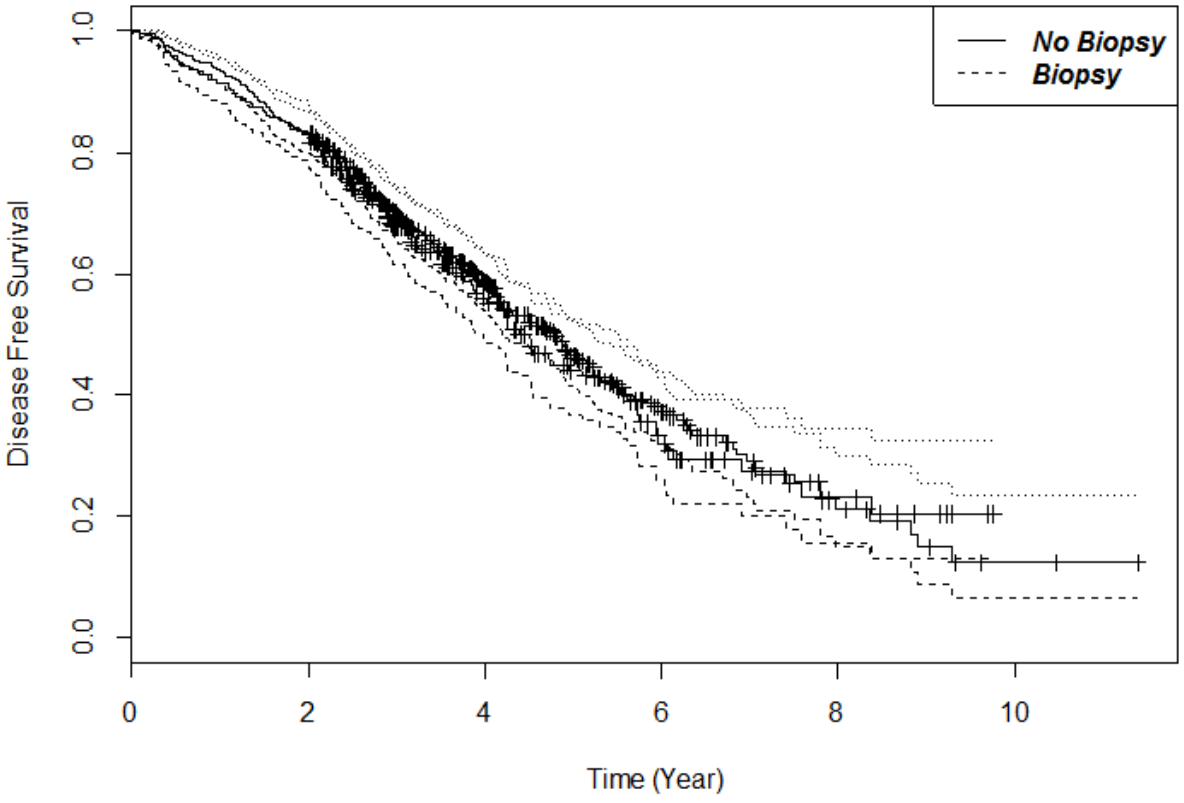
0.2
0.4
0.6
0.8
1.0
0
2
4
6
8
10
Time (Year)


No Biopsy
Biopsy
Disease Free Survival
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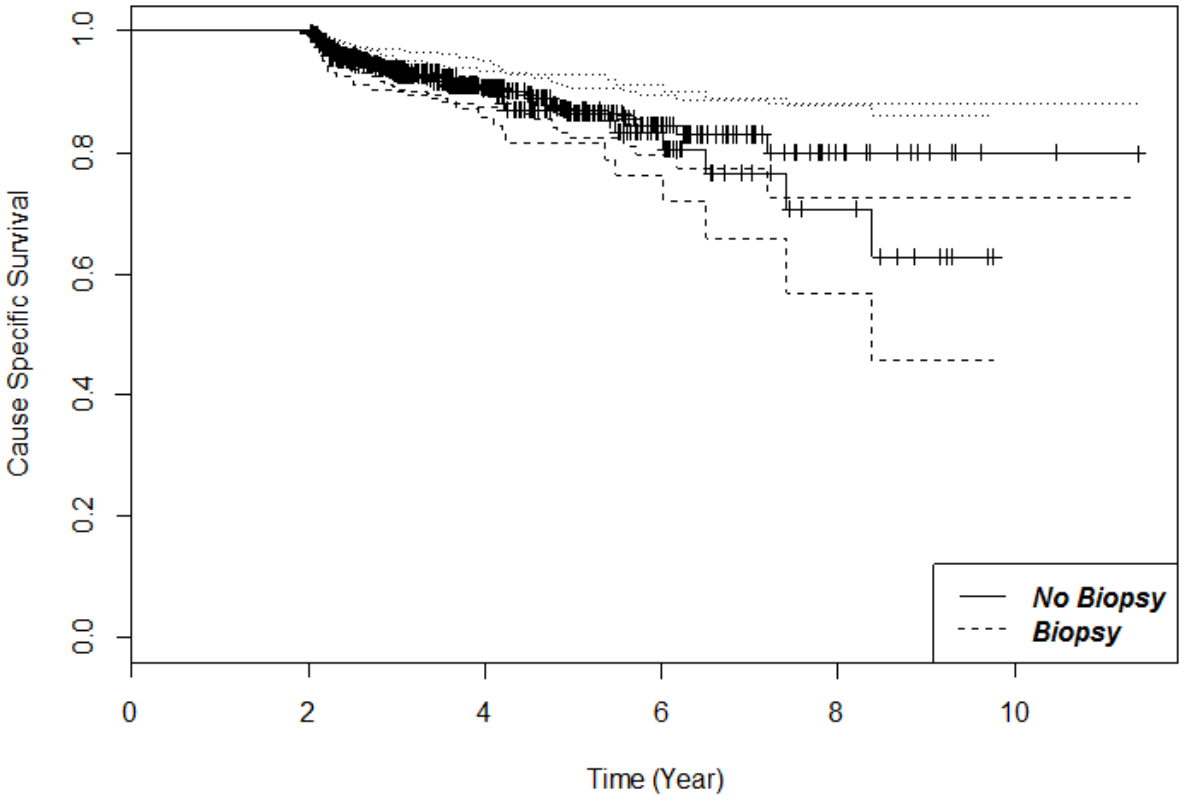
0.4
0.6
0.8
1.0
0
2
4
6
8
10
Time (Year)


Cause Specific Survival
0.0
0.2
0.4
0.6
0.8
1.0
0
2
4
6
8
10
Time (Year)
No Biopsy
Biopsy